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Abstract: Oxytocin manipulation has been implicated in the facilitation of social and cooperative behaviours, either through increasing positive and cooperative social interactions, or facilitating bond formation. Here we aimed to determine whether peripheral administration of oxytocin would affect the propensity of unrelated female house mice (Mus musculus domesticus) to cooperate. In order to investigate this we used female house mice, with their cooperative ability to communally nurse offspring. Pairs of unfamiliar females received intraperitoneal injections of oxytocin over a three-day cohabitation period. Following this initial phase, a male was introduced and they were allowed to reproduce. We monitored how long it took females to establish and successfully cooperate in the raising of a communal litter. Oxytocin did not affect the females' ability to reproduce. However, oxytocin treated females took significantly longer to establish a successful communal litter (with pups of both partners being weaned) than saline treated control females. This delay in communal nursing was due to higher pup mortality and loss of first-born litters in the oxytocin group during their first reproductive event. We conclude that administration of exogenous oxytocin during the early stages of the female relationship delays the tendency of female house mice to affiliate and cooperate in the formation of a communal litter. Our findings contribute to the growing field of oxytocin based studies and sheds light on the potential long term effects of oxytocin during early pairwise social interactions.

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Oxytocin Administration During Early Pair Formation Delays Communal Breeding in Female House Mice

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12 HIGHLIGHTS

13

14 • We compared communal breeding in OT and control treated wild-derived female house mice

15 • OT delayed successful communal rearing of litters

16 • Delayed cooperation was due to lower pup survival in 1st born OT communal litters

17 • We hypothesise that OT effects are time sensitive

18

Oxytocin manipulation has been implicated in the facilitation of social and cooperative behaviours, either through increasing positive and cooperative social interactions, or facilitating bond formation. Here we aimed to determine whether peripheral administration of oxytocin would affect the propensity of unrelated female house mice *(Mus musculus domesticus)* to cooperate. In order to investigate this we used female house mice, with their cooperative ability to communally nurse offspring. Pairs of unfamiliar females received intraperitoneal injections of oxytocin over a three-day cohabitation period. Following this initial phase, a male was introduced and they were allowed to reproduce. We monitored how long it took females to establish and successfully cooperate in the raising of a communal litter. Oxytocin did not affect the females' ability to reproduce. However, oxytocin treated females took significantly longer to establish a successful communal litter (with pups of both partners being weaned) than saline treated control females. This delay in communal nursing was due to higher pup mortality and loss of first-born litters in the oxytocin group during their first reproductive event. We conclude that administration of exogenous oxytocin during the early stages of the female relationship delays the tendency of female house mice to affiliate and cooperate in the formation of a communal litter. Our findings contribute to the growing field of oxytocin based studies and sheds light on the potential long term effects of oxytocin during early pairwise social interactions.

Key words: Cooperation; Communal nursing; House mice; Peripheral oxytocin

The oxytocinergic system has been implicated in the facilitation of a variety of social and cooperative behaviours as well as the suppression of the stress response (C. S. Carter et al., 1992; G. G. Carter and Wilkinson, 2015; Crockford et al., 2014; 2013; McCarthy, 1990; Mooney et al., 2014; Popik et al., 1992; Smith et al., 2010; Witt et al., 1990; Wittig et al., 2014). Over the last couple of decades evidence for the role of the peptide hormone oxytocin (hereafter: OT) in the facilitation of social bonding, affiliative and cooperative behaviours has accumulated in a range of species (Anacker and Beery, 2013; Beery and Zucker, 2010; G. G. Carter and Wilkinson, 2015; Crockford et al., 2013; Mooney et al., 2014; Wittig et al., 2014). While central administration of OT was thought to be essential, current evidence indicates that peripheral administration also induces behavioural effects (McCarthy, 1990; McCarthy et al., 1986; Mooney et al., 2014; Popik et al., 1992; Smith et al., 2010), which has simplified manipulations in less traditional species (such as primates and humans). Studies include virgin and pregnant female house mice (*Mus domesticus*) which demonstrated decreased infanticide behaviour towards pups placed in their homecage after subcutaneous injection with OT (McCarthy et al., 1986); and female prairie voles (*Microtus ochrogaster*) which demonstrated a preference for a previous male cohabitation partner after receiving peripheral pulses of OT (Cushing and C. S. Carter, 2000). Additionally, huddling and partner seeking behaviour was facilitated by intranasal OT in male and female marmosets (*Callithrix penicillata*, Smith et al., 2010). In the context of cooperation, subcutaneously injected OT increased a range of cooperative behaviours including pup feeding, digging and guarding behaviours in wild meerkats (*Suricata suricatta,* Madden and Clutton-Brock, 2011), and intranasal administration of OT increased time spent allogrooming in the common vampire bat (*Desmodus rotundus,* G. G. Carter and Wilkinson, 2015). Furthermore, elevated OT levels were found in chimpanzee urine following socio-positive or cooperative interactions, such as food sharing with conspecifics (Wittig et al., 2014) and grooming with a preferred partner (Crockford et al., 2013).

To summarise, many results from studies investigating the effects of OT provide evidence that OT increases positive perceptions and social motivation (Crockford et al., 2014; Cushing and C. S. Carter, 2000; Madden and Clutton-Brock, 2011; McCarthy, 1990; Mooney et al., 2014; Smith et al., 2010). However, despite its ability to amplify pre-existing positive social perceptions it can also

68 intensify negative ones (Beery, 2015; Crockford et al., 2014; De Dreu et al., 2012) and be context and
69 partner specific (Bartz et al., 2011; Beery, 2015; Campbell, 2008; Crockford et al., 2013; Cushing and
70 C. S. Carter, 2000; Cushing et al., 2001; Declerck et al., 2010; Wittig et al., 2014). Negative effects of
71 OT have been found in capuchin monkeys that demonstrated reduced cooperative food sharing
72 behaviour after receiving intranasal OT (Brosnan et al., 2015), and female house mice exhibited no
73 preference for a previous cohabitation partner after intraperitoneal injection of OT (Harrison et al.,
74 2016). Furthermore, humans who received intranasal OT demonstrated increased envy (Shamay-
75 Tsoory et al., 2009), decreased cooperation when social information was lacking (Declerck et al.,
76 2010), and in studies where subjects were confronted with an unreliable partner OT lost its trust
77 enhancing effects (Mikolajczak et al., 2010). Whether through its positive or negative actions, OT is a
78 prime candidate for having a role in intra-sexual cooperation. In particular, we were interested in
79 whether OT plays a role in the ability of females to cooperate through communal offspring care, thus
80 affecting individual fitness.
81 To explore such notions, female house mice offer an ideal study system as they have been
82 shown to cooperate by nursing communally in a range of different settings including the laboratory,
83 semi-natural and wild environments (Manning et al., 1992; Sayler and Salmon, 1971; Weidt et al.,
84 2014; Wilkinson and Baker, 1988). When forming a communal litter females raise their offspring in
85 the same nest or shelter and once litters are pooled females do not distinguish between their own and
86 non offspring (Hayes, 2000; König, 1994a; 1989; Packer et al., 1992). Therefore, females will
87 cooperate in the care of their young by nursing all offspring in a nest indiscriminately (Ferrari et al.,
88 2015; König, 1994b; 1989). Female mice often form such egalitarian relationships with familiar
89 sisters leading to increased lifetime reproductive success for both females (König, 1994b). However,
90 females also form individual preferences for unrelated individuals when kept in laboratory enclosures
91 (Weidt et al., 2008), where they will communally nurse even when given the option to rear litters
92 alone. Communal nursing provides many benefits for females such as allowing them to wean more
93 offspring in their lifetime (König, 1997), and provides the opportunity to spend more time foraging, as
94 their partner attends the litter in their absence (Auclair et al., 2014). However, free-living females will
95 also nurse their pups solitarily (raise pups alone) despite having potential communal nursing options

available to them (Weidt et al., 2014). This suggests that there is an element of choice and additional factors involved when deciding whether or not to communally nurse, and with whom.

In this study we aimed to determine whether OT influenced a pairs ability to cooperate during communal nursing. In order to do so we experimentally increased peripheral OT in pairs of unrelated, unfamiliar female house mice over three days, before introducing a male. In contrast to familiar sisters, unrelated unfamiliar females vary in their propensity to communally nurse with a randomly assigned female partner in an experimental situation (König, 1994a; Palanza et al., 2005). If OT has a positive effect on early female social relationships that results in reproductive cooperation, we would expect to see this when treating pairs of unrelated, previously unfamiliar females. After the intial treatment, females were allowed to reproduce and we monitored how long it took them to establish and successfully wean a communal litter.

We recently found evidence suggesting that OT treatment prevents or lessens the formation of a preference for a cohabitation partner in female house mice (Harrison et al., 2016). Given these current findings and those of studies where OT was found to reduce cooperation, we predicted that females in the OT treatment would take longer to nurse communally than CON females, indicating a decreased propensity to cooperate.

METHODS

We used wild derived, laboratory born F1 to F3 descendants of house mice (*Mus musculus domesticus*) originating from a barn population near Zurich, as described in König and Lindholm (2012). Weaning occurred at day 23 and subsequently animals were kept in same-sex sibling groups until 11-14 weeks of age, when females were sexually mature and the OT system was well developed (in rodents, the OT system is already developed at weaning (Yamamoto et al., 2004)). Cages contained standard animal bedding (Lignocel Hygienic Animal bedding, JRS), with cardboard and tissue provided *ad libitum* for bedding and shelter. Mice were kept under a constant light-dark cycle of 14:10 hours (lights on at 5.30 am CET, with a half hour dawn and dusk phase at the beginning and end of the light phase), at a temperature of 22-24°C and humidity of 50-55%. At all stages of the

experiment, food (laboratory animal diet for mice, Provimi Kliba SA, Kaiseraugst, Switzerland) and water was provided *ad libitum*. Animal use and experimental design were approved by the Veterinary Office Zurich, Switzerland (Kantonales Veterinäramt, Zurich, no. 34/2014).

Experimental Procedures

Pairs of virgin unfamiliar, unrelated females (pairs did not share the same parents) were randomly assigned to one of two treatment groups, oxytocin (OT, $N = 14$ pairs) or saline control (CON, $N = 14$ pairs), and both females in a pair received the same treatment. Female pairs were matched, as best as possible, in age (age difference: 5.0 ± 0.6 days, mean ± SE) and weight (weight difference: 2.1 ± 0.3 g, mean ± SE). For identification females were marked with different ear punches.

At the beginning of the experiment, each female was housed in a Makrolon Type II cage (18 cm wide, 24 cm long and 14 cm high) for 30 minutes, equipped with a transparent plastic tube (4 cm diameter) that would allow access to the partner female's cage. Entry to the neighbouring cage was initially prevented with a removable barrier. Both females in the pair were then given an intraperitoneal injection of their treatment, on each of three consecutive days between 4 pm and 6 pm. Following each injection females were allowed a fifteen-minute recovery period in their own cage, the barrier was then removed allowing each female of a pair access to both cages and to freely interact. On the fourth day, the morning after the third injection, an unrelated male (not sharing a parent with any of the two females) was introduced. The male's home cage, a third Type II cage, was connected with a transparent tube, in line with the two female cages. The two females and the male thereafter had access to all three cages and we refer to the three mice sharing a cage system as a group.

Throughout the experiment cages were checked daily for any signs of aggression among the mice; in the event of excessive aggression, resulting in wounds, groups were separated. Once a day we determined whether or not females were resting together in a nest (side-by-side contact, a measure of affiliation) to determine if the treatments differed in occurrence of this behaviour. We compared

days before litters were born and in the presence of pups, until at least one litter was weaned. Nineteen days after the introduction of the male, cages were additionally checked daily for birth of litters (house mice have a gestation period of 19-21 days, (König, 2012)). Assignment of a litter to a mother was based on visual inspection (lack of body swelling of a previously pregnant female) and on a decrease in female body weight. In order to avoid any bias groups were checked blind to treatment group. Once a litter was born, females and pups were weighed on set days following birth until weaning [day 1 (birth), 5 (pups only), 9, 13, 17 and 23] when the pups were removed. Additional features were determined including litter size and sex ratio. These measurements allowed us to determine any pup mortality and monitor condition of the mice throughout. In a previous experiment female pairs received identical OT treatment and socio-positive and -negative behaviours were monitored in a series of focal observations, over a 3-day cohabitation period (Harrison et al., 2016). Results from this study indicated no significant difference in behaviours between OT and CON treated females, therefore in the current study these detailed behavioural observations were not made.

A communal litter in this study was determined when the second female gave birth within 16 days of the first female and pups were raised in a single nest (this definition has been used in other studies (Ferrari et al., 2016; König, 1994b)). Day 16 was chosen as weaning commences one day later when pups begin to eat solid food and reduce milk consumption (König and Markl, 1987). Since offspring of 17 days or older have only a small influence on female investment we no longer considered this as a communal litter. A successful communal litter was determined if at least one pup from each litter was weaned (day 23), and pups had been nursed by both females. An unsuccessful communal litter was classified if a second litter was born within 16 days of the first, but no pups or only pups from one of the litters survived until weaning. A solitary litter was defined when pups were born in the absence of another un-weaned litter and when no other litter was born within 16 days.

Once each pair had successfully weaned a communal litter the experiment was complete. However, if a pair did not successfully wean a communal litter within three months from the date the male was introduced, the experiment was terminated and the pair considered unsuccessful. In order to calculate the latency until formation of the first communal litter we calculated the number of days, starting from the day the male was introduced, until the second female gave birth (only when the first

female had given birth no more than 16 days before and the pups were pooled together in the same nest).

Within a communal litter, under our previous definition, litters can differ by up to 16 days in age (Ferrari et al., 2015; König, 1994b), and when heavily pregnant the female giving birth second in a communal litter may kill some or all of her partners young before giving birth herself (Ferrari et al., 2016; König, 1994b, such infanticide has never been observed after offspring reached 17 days of age). To assess the effect of such behaviour on overall pup survival we classified litters into three birth order (the order females gave birth) categories; first-born: the first born litter in a communal litter (no other litter born in the previous 16 days); second-born: a litter born within 16 days of the first born litter and if no other litter was born within 16 days thereafter; and middle-born (when necessary): a second litter born within 16 days of the first litter (with at least one pup surviving until weaning) and another litter was born within 16 days of the second litter.

Peptide and Doses

Synthetic oxytocin (Product: O4375-250IU, Sigma Aldrich Co., Germany) was dissolved in sterile saline (0.9% NaCl, Bischel) to give a concentration of 0.12 (or 2 IU) mg/ml (approximately 0.6 mg/kg). Subjects on each of three testing days received an intraperitoneal injection of either OT or CON. Half of the animal pairs (N = 14) received OT (0.012 mg OT / 0.1 ml saline) and the remaining pairs (N = 14) received an equivalent dose of isotonic saline (0.1 ml). Both females in a pair received the same treatment. Dosage of OT was derived from a study where a peripheral injection of OT led to increased circulating OT for up to 2 hours and a peak in brain dialysates 30 minutes after administration (Neumann et al., 2013). The same dosage and/or route of administration have also been used in other studies with house mice and different rodents with effects on behaviour (Harrison et al., 2016; Mooney et al., 2014; Peñagarikano et al., 2015).

Statistical Analysis

Statistical tests were carried out using R version 3.1.3 (R core team, 2015). Linear (LM) models were used unless the data required random effects to control for repeated measures (more than one litter per female or to identify the pair). In these cases, linear mixed models (LMM) and/or generalised linear mixed models (GLMM) were required and analysed using the 'lme4' package in R (Bates et al., 2014). Where appropriate we assessed for normality of model assumptions visually using diagnostic plots and in the event that they were not fulfilled data were transformed (Table 1). Models using a binomial error distribution were tested for overdispersion. Model selection was carried out to find the best model using the full model and comparing it to all lower models using the model selection function in the 'MuMIn' package (Bartoń, 2015). Models were ranked by corrected Akaike information criterion (AICc) values and the most adequate model was the one with the lowest AICc value. In the event that two or more models fell within two delta AICc of each other they were considered equal and therefore the model with the lowest degrees of freedom was chosen.

Table 1. Summary of all models used in the data analysis. Included are the fixed effects used in the full model and the most adequate (best) model after model selection. Any transformations and error distributions are also stated.

Type of model	Response variable	Fixed effects:		Random effects:
		Full model	Best model	
OT effects on propensity to nurse communally				
1. LM (log)	Latency to birth of succ CL	trt * wdf + adf	trt	
2. LM	Latency to first CL born	trt	Intercept only	
Effect of treatment on litter attributes				
3. LMM	Litter size at birth	trt * litnum	litnum	PairID/MotherID
4. LMM	Litter size at weaning	trt * litnum	litnum	PairID/MotherID
5. LMM	Weaning weight of pup	trt * **ord** + lsw + adp	Intercept only	PairID/MotherID, LitterID
OT effect on pup survival				
6.GLMM (binomial)	Proportion of pups survived	trt * ord + adp	ord	PairID/MotherID
7.GLMM(binomial)[a]	Proportion of pups survived[a]	trt * ord + adp	trt * ord	PairID
8.GLMM (poisson)	Number of pups killed[a]	lsb + lsp + trt	Intercept only	PairID

List of abbreviations: CL = communal litter. succ = successful CL (at least one pup from each litter survived until weaning). trt = Treatment (OT or CON). adf = age difference between the two females. wdf = weight difference between the two females at the beginning of the experiment. litnum = a female's litter number, whether it was her first, second etc. ord = birth order in a CL (first-, second- or middle-born litter – not included

in §). adp = age difference between the two litters in the CL, $\left[\sqrt{(age\ of\ focal\ litter - age\ of\ other\ litter)^2}\right]$. lsw = litter size at weaning. lsb = litter size at birth of first litter born in a CL. lsp = litter size of the second female to give birth in a CL. MotherID = ID of the mother that gave birth. PairID = the pair that the females belonged to. LitterID = the litter the pup belonged to. § Pup survival for first CL only (successful or unsuccessful). # First-born litter in the CL only (successful and unsuccessful CL).

Table 1 illustrates all models used to analyse the effect of treatment on the females' propensity to nurse communally, as well as on litter sizes and pup mortality. Response variables and fixed effects are provided for the full models and most adequate models, where required random effects are also stated. We further used a poisson GLMM to determine whether number of days resting in side-by-side contact differed by treatment and in the presence of pups, pair ID was included as a random effect. To determine the significance of the fixed effects for the most adequate model only we used likelihood ratio tests for GLMM and LMM (Crawley, 2007), and F tests for LMs. Fixed effects that were not included in the most adequate model were defined as non-significant and therefore no *P* values are provided. In the case of pup survival for the first communal litter, *post-hoc* analysis was carried out on the interaction term to better understand within interaction effects, we used manually assigned contrasts in the 'multcomp' package in R (Hothorn et al., 2008). Additionally, we used a Chi-squared test (effect size given as Φ) to determine if there was a difference in the total number of communal litters born by treatment.

RESULTS

Initially 28 pairs (*N* = 56 females) were included in the experiment, 14 pairs per treatment. Of these 28 pairs, four were excluded due to aggressive males or incompatible females before reproduction commenced (two pairs from each treatment). Aggression, due to incompatibility, between unfamiliar females leading to separation is not an unusual occurrence (König, 1994b; Weidt et al., 2008). Therefore, 24 pairs (12 per treatment) were included in the final analysis. Of these 3

pairs (1 CON, 2 OT) were separated after birth of the first litter due to male aggression towards one or both females, therefore for some analyses these pairs were not included (excluded from models 1 and 6, Table 1 and Chi squared test).

OT Effect on the Propensity to Nurse Communally

In total 68 litters were born to the 24 pairs of females (12 per treatment) of which 32 litters were successfully raised and weaned as communal, 9 by CON pairs (18 litters) and 7 by OT pairs (14 litters). The remaining 3 CON and 5 OT pairs failed to successfully raise a communal litter within 3 months (Table 2). In total, there were 17 unsuccessful communal litters (N = 34 litters); in 3 cases both litters were lost completely and in 14 cases only the first-born litter was lost completely. Three litters (2 OT, 1 CON) were raised solitarily (where no other litter was born with in 16 days) and 1 litter was born solitary but not weaned. In two pairs there were overlapping litters (middle-born), these litters were then counted twice, firstly as an unsuccessful communal litter (first-born: A1, middle-born: A2) and then as a successful communal litter (middle-born: A2, second-born: A3). This means the number of litters accounted for was 70 but only 68 separate litters were born. On one occasion both females in a pair (CON) gave birth on the same day, which precluded determination of birth order, we therefore allocated half the pups to each female; all of these pups were found dead (N = 14 pups).

Table 2: Information on all the litters born by treatment. Numbers are given as the total for the 12 pairs by treatment, except when stated with * where they are out of the total communal litters (CL).

	OT	CON
First CL successful	1	7
Number of first litters that failed[#]	9	4
Number of second litters that failed[#]	0	3
Number of pairs with a successful CL	7	9
Number of pairs that had more than one attempt at forming a successful CL	6	3
Total number of pairs	12	12
Number of CL*	18	15
Number of unsuccessful CL*	11	6

[#]First and second litter born to each pair, number that suffered complete loss of pups on first communal litter (CL)

Female pairs who had received OT took significantly longer to successfully rear a communal litter than CON pairs (LM: $F_{1,14} = 8.72$, $P = 0.010$, Fig.1); the latency (mean ± SE) in days from introduction of the male was 51.71 ± 5.32 days for OT females and 30.67 ± 4.85 days for CON females. However, there was no significant difference between treatments in the latency until birth of the first communal litter, whether successful or unsuccessful (LM: $F_{1,19} = 1.75$, $P = 0.202$, Fig. 1), the mean (± SE) latencies for OT: 29.64 ± 3.94 days and CON: 23.90 ± 0.32 days. There was also no significant difference in the number of communal litters born, successful and unsuccessful combined (Chi-squared test: $\chi_1^2 = 1.27$, $P = 0.261$, $\Phi = 0.21$, N = 30). There was no significant difference between treatments (GLMM: $\chi^2(1) = 1.03$, $P = 0.320$) in number of days females were observed resting together, however in the presence of pups pairs spent significantly less time resting in side-by-side contact than during the time before a litter was born in both treatments (GLMM: $\chi^2(1) = 4.15$, $P = 0.042$). Females never established separate nests or had litters in separate nests.

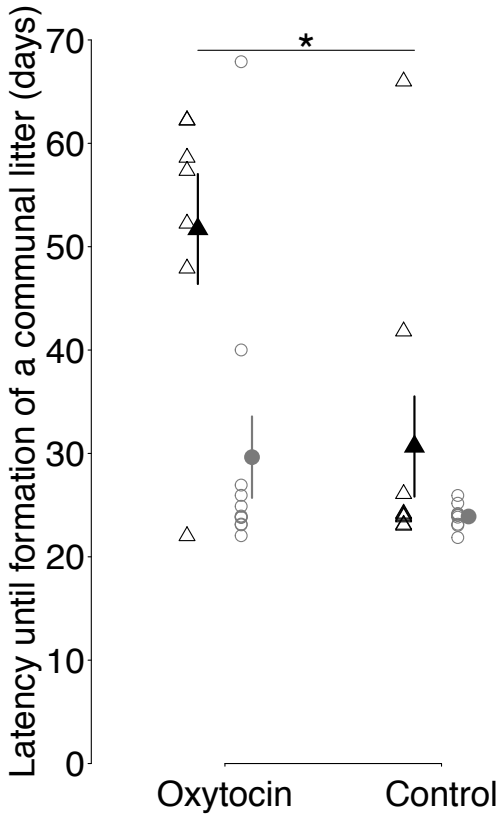

Figure 1. Latency until the birth of the first communal litter and birth of the first successful communal litter. The latency until formation of the first successful communal litter (black, triangles), and the latency until the first communal litter was born whether successful or unsuccessful (grey, circles). Shown for both treatments (mean ± SE). OT pairs took significantly longer to form a successful communal litter * $P = 0.01$, but there was no significant difference in the latency to the first communal litter attempted ($P = 0.20$).

OT Effect on Pup Survival

From the 68 litters born there were 418 pups, of which 240 (57.4%) survived until weaning. Pup survival overall was 59.9% in the OT group and 53.8% in CON group. First-born litters experienced complete or partial loss of pups in 34 of 37 (91.9%) litters compared to only 8 of 27 (29.6%) second-born litters. In the OT group 10 of 18 (61.1%) first-born litters in a communal litter suffered a complete loss of pups compared to 6 of 15 (40.0%) first-born litters in the CON group. Furthermore, 58.3% of first attempts of communally nursed litters were successful in CON pairs

315 compared to 8.3% of OT pairs (Table 2). We were able to monitor litter loss (infanticide) as pups
316 were typically found with their head bitten off or wounds to the neck region. Infanticide is common in
317 pregnant female house mice (McCarthy and Saal, 1985), and pregnant females often kill pups already
318 present in the nest before giving birth themselves (Ferrari et al., 2016; König, 1994b).
319 For all litters born there was no overall effect of treatment on pup survival but there was a
320 significant effect of birth order (GLMM: $\chi^2(2) = 22.48$, $P < 0.001$), where pups from first-born litters
321 had a lower probability of survival than pups from second- and middle-born litters. There was no
322 significant effect of age difference between the two litters. Additionally, we analysed pup survival in
323 the first communal litter attempt only (this included successful and unsuccessful communal litters) for
324 each pair, to assess whether this had an influence on the latency until formation of the first successful
325 communal litter. We found a significant interaction between treatment and birth order (GLMM: $\chi^2(1)$
326 $= 4.44$, $P = 0.035$), and *post hoc* analysis revealed that in the OT group only pups from the first-born
327 litter had a significantly lower survival probability than pups from the second-born litter ($z = 4.15$, $P <$
328 0.001, Fig. 2). There was no significant difference in survival between first-born and second-born
329 litters of the CON group ($z = 2.12$, $P = 0.067$). However, there was a tendency for lower survival in
330 first-born CON litters, this was in accordance with the overall effect of birth order in model 6 (see
331 Table 1).
332
333

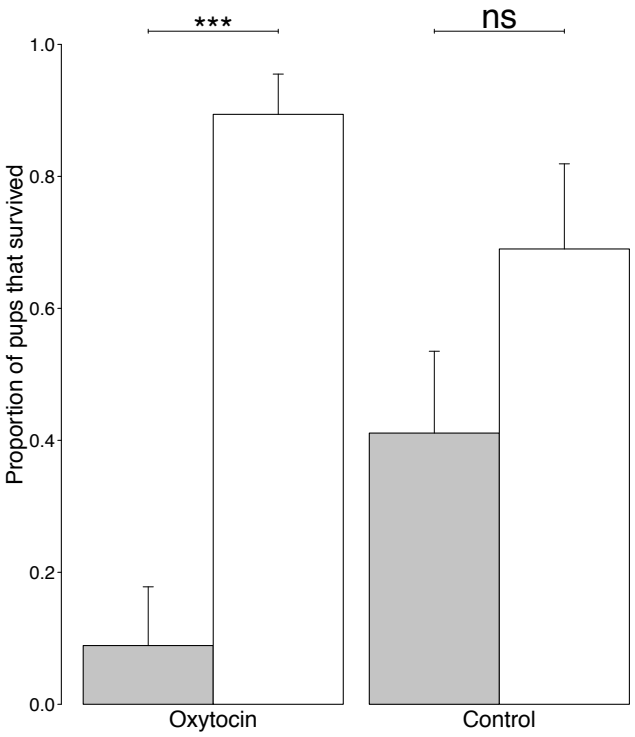

Figure 2. Proportion of pups that survived in the first- and second-born litters of the first communal litter for each pair. The proportion of pups that survived in the first communal litter only (both successful and unsuccessful communal litters), first-born (grey), and second-born (white) litters by treatment, given as mean ± SE, there was a significant interaction of treatment by birth order, *** < 0.001.

We additionally examined the number of pups killed in the first litter of each communal litter (successful and unsuccessful) and found no significant effect of litter size of the first-born litter, litter size of the female about to give birth, or treatment.

Effect of Treatment on Litter Attributes

Pups born in the OT groups did not differ significantly in weaning weight from pups born in the CON groups (LMM: χ^2 (1)= 1.82, P = 0.177), tested as the weaning weight for each pup born (average weaning weight ± SE: OT: 10.7 g ± 0.1 and CON: 11.7 g ± 0.1). Weaning weight was not significantly affected by litter size at weaning or age difference between the litters. Furthermore, there

was no significant effect of treatment on litter size at birth (average litter size at birth (all litters born): OT: 6.7 ± 0.4 pups and CON: 5.9 ± 0.3 pups, here mean ± SE) or weaning (average litter size at weaning: OT: 4.0 ± 0.6 pups and CON: 3.1 ± 0.5 pups), but with increasing number of litters born to a female litter size significantly increased at birth (LMM: χ^2 (1)= 7.85, P = 0.005) and weaning (LMM: χ^2 (1)= 8.94, P = 0.003). This reflects the observation that primiparous females give birth to smaller litters than multiparous females (König and Markl, 1987).

DISCUSSION

In this study we determined whether administration of peripheral OT influenced the ability of unfamiliar female pairs to cooperate through communal nursing. Our findings showed that pairs of females treated with OT shortly before and during the initial phase of cohabitation took significantly longer to form a successful communal litter in which both females weaned at least one offspring. On the one hand, this was surprising given that past studies investigating the role of OT on social and affiliative behaviours predict that individuals with elevated OT would have an increased likelihood to cooperate (De Dreu, 2012; Madden and Clutton-Brock, 2011; Wittig et al., 2014). On the other hand, our most recent study (Harrison et al., 2016) suggested that OT administered during first encounters (using the same approach as the current study) delays or lessens the formation of a preference for a previously unknown partner. Therefore, our results suggest that OT treatment did delay the tendency of female house mice to cooperate in the formation of a communal litter.

OT Delays Communal Nursing

Female pairs did not differ significantly in days spent resting in side-by-side contact prior to parturition and aggression levels were low in both treatments. While we did not specifically monitor other female behaviours prior to parturition in this study, results from a previous study Harrison et al. (2016) demonstrated, during an identical three days of cohabitation and treatment, no significant difference between OT and CON treated female pairs with regard to socio-positive and -negative

379 behaviours. Only 3 pairs (2 OT, 1 CON) exhibited aggression towards each other during pregnancy or
380 after birth of the first litters leading to separation. Female house mice are generally social but
381 aggression between pairs has been shown to impair cooperation (Rusu and Krackow, 2004), and
382 competition over reproduction results in agonistic behaviour (König, 1994b; König and Lindholm,
383 2012; Palanza et al., 2005; Rusu and Krackow, 2004). These observations, taken together with the
384 findings of Harrison et al. (2016), provide little evidence to suggest that there was a difference
385 between treatments with regard to affiliative or intolerant behaviour. Furthermore, OT administration
386 did not impact the females' ability to reproduce, as time until birth of the first litter did not differ by
387 treatment. Past research confirms this as mice whose OT receptor gene was inhibited were still able to
388 function reproductively and gave birth (Russell and Douglas, 2003; Veening et al., 2014).
389 Interestingly, OT females took longer to successfully wean a communal litter. This was not
390 because OT females raised their litters solitarily (for example, by using the different cages accessible
391 to the group), or because they differed in the number of communal litters attempted (successful and
392 unsuccessful combined) when compared against the CON. Females in the OT group did have
393 potential communal litters as both females gave birth within sixteen days of each other. Our results
394 showed that this delay in cooperation was most apparent during the first communal nursing attempt,
395 as a higher number of first-born litters failed (complete loss of pups) in the OT group compared to the
396 CON. Additionally, pup survival in this first attempt of a communal litter was significantly lower in
397 the first OT litter compared to the second, which was not the case in the CON, suggesting OT litters
398 suffered higher levels of initial pup mortality. Therefore, before another attempt of a communal litter
399 could be made females had to wait for gestation time and birth intervals, which led to an increased
400 latency of on average 31 days until a successful communal litter was established. This could suggest
401 that OT females had a reduced propensity to cooperate through communal nursing.
402 Why did administration of OT during the first three days of cohabitation lead to increased pup
403 mortality and delayed cooperation in female house mice? Past studies have shown OT to be related to
404 increased maternal aggression towards intruders postpartum (Bosch, 2013; Bosch and Neumann,
405 2012; Ferris et al., 1992). However, this is often due to naturally elevated OT levels released during
406 lactation and the onset of maternal behaviour (Ferris et al. 1992; reviewed in: Bosch 2013). Given that

407 in the current study we administered OT when females were virgin it is less likely that OT has acted
408 directly on maternal aggression. Therefore, any elevated maternal aggression could be analogous to
409 the natural behaviour of females postpartum. Especially as female house mice are known to kill pups
410 of another female when heavily pregnant (Ferrari et al., 2016; König, 1994b; 1994a; McCarthy et al.,
411 1986). Alternatively, females have been shown to kill own pups under stressful situations (Poley,
412 1974). As pups were found dead we could not be certain which female committed the infanticide,
413 therefore we cannot rule this out as a possibility.
414 In contrast to our findings, McCarthy et al. (1990) found that subcutaneous OT injection
415 decreased infanticide behaviour in virgin and pregnant female house mice when a pup was placed in
416 their home cage. However, while in that study behaviour towards pups was assessed shortly after OT
417 administration, in our study OT was administered during early female social interactions prior to
418 pregnancy, not during or shortly before initial encounter with pups. The initial higher infanticide
419 observed among OT females here may therefore be linked to increased female competition (Palanza et
420 al., 2005), or a reduced incentive to cooperate. Alternatively OT could have increased social
421 recognition in the females (Bartz et al., 2011; Bielsky and Young, 2004; Ferguson et al., 2001; 2000),
422 which may have reinforced recognition of own pups. This could suggest that the timing of OT
423 administration in house mice may have different implications on infanticide behaviour.
424 It has been suggested that OT effects are likely dependent on the characteristics of the
425 situation and the interaction partners present (Bartz et al., 2011; Crockford et al., 2014; Wittig et al.,
426 2014). Declerck and colleagues (2010) suggested that when appropriate social information about a
427 partner was lacking OT could diminish cooperation. Additionally, if a partner was believed unreliable
428 OT might lose its trust enhancing effects (Mikolajczak et al., 2010). In our study, the first OT
429 administration happened prior to any female interaction meaning that females had no prior social
430 information on their new partner. In accordance to the suggestion by Declerck et al. (2010), we found
431 a diminished propensity to cooperate amongst these females, which could indicate that the timing of
432 administration was critical in determining how OT impacted cooperative behaviours. Additionally,
433 females treated with OT in an identical initial set-up demonstrated a lack of preference for their
434 cohabitation partner relative to a novel partner (Harrison et al., 2016). In house mice, sharing a group

with a preferred social partner is important for successful cooperation and associated with higher lifetime reproductive success than being experimentally grouped with a previously un-preferred partner (Weidt et al., 2008). In the present study, this lack of preference may also occurred between the females treated with OT, and may not have allowed for the reinforcement of socio-positive behaviours, which could explain the delay in communal litter formation and high infanticide.

OT as Cause Versus Consequence in Partner Preference Formation

Beery and Zucker (2010) showed that OT was not required for initial formation of a preference in female meadow voles, and Peñagarikano et al. (2015) found that OT treated wild type mice did not differ significantly from a control group in time spent socially interacting on initial encounter with a stranger. Therefore, assuming that increased circulating OT levels are not the cause but the consequence of interacting with preferred social partners (Crockford et al., 2013; Wittig et al., 2014), we hypothesise that its effects are time sensitive and partner specific. For example, OT levels were elevated in chimpanzee urine after grooming with a preferred partner (Crockford et al., 2013), blood OT levels increased in dogs after short-term positive interactions with their owner (Handlin et al., 2011), and plasma OT levels increased in children after physical contact with their mothers (Fries et al., 2005). Therefore, an increase in OT induced by a preferred or familiar social partner could result in an increased propensity to cooperate only with that social partner. In our study, OT was administered prior to initial encounter with the other female meaning that the elevated peripheral levels were not a result of social interactions with the new partner. In essence, this could mean the female did not consider this partner as "trustworthy" or a preferred partner.

In contrast, studies in humans have shown that OT may also become elevated after contact with a stranger or unfamiliar individual, since mothers had higher urine OT levels following interaction with an unfamiliar child than when interacting with their own biological child (Bick and Dozier, 2010). Additionally, Morhenn et al. (2008) found that circulating OT levels increased after receiving a massage but only when it was followed by an act of trust by a stranger. Plasma OT levels also increased in females who did not suffer from relationship anxiety following a relaxation massage

given by a stranger (Turner et al., 1999), thus indicating that some OT-induced responses may be species specific and potentially dependent on the social system being studied.

To better understand these concepts, future studies could test the hypothesis of an OT effect of partner specificity by allowing previously unfamiliar and unrelated female mice to initially familiarize before administering OT and then testing for a partner preference. In such a scenario, we would then predict that OT administration would result in improved cooperation among these familiar partners when compared to controls.

Influence of OT on Maternal Investment in Pups

We found no treatment effect on litter size at birth or weaning. In group living female house mice uneven litter size at birth has been demonstrated to decrease the propensity of sisters to cooperate when they attempt to avoid exploitation from having the smaller litter (Ferrari et al., 2016). As we found no effect, it is unlikely that this was a contributing factor towards the decreased cooperation. We also found no effect of litter size of the first-born litter and of the female about to give birth on the number of pups killed in the first litters. Additionally, we found no effect of treatment or age difference between the litters on weaning weights of pups suggesting that females, although differing in the latency until formation of a successful communal litter, did not differ in their investment to the pups once present. This supports findings that suggest females invested according to the combined communal litter size (Ferrari et al., 2015). Therefore, our previous findings on reduced partner preferences for a cohabitation partner in OT treated females (Harrison et al., 2016) combined with the current findings of increased infanticide, indicate that OT had an effect on the propensity of females to cooperate.

Conclusions

Our findings suggest that administration of exogenous OT during the early stages of female relationships appeared to have delayed effects on their propensity to cooperate. Female treatment had

no effect on the ability to reproduce, as we found no difference in time until birth of first litters. However, OT treated females took longer to successfully establish and wean a communal litter, this was due to the higher rates of pup mortality (via infanticide) in the first litter produced.

In sum, these findings add to the growing number of studies that have also found conflicting results in relation to the effect of OT on social and cooperative behaviour (Bales et al., 2013; Beery, 2015; Brosnan et al., 2015; Harrison et al., 2016; Peñagarikano et al., 2015), and support findings that suggest OT effects can be very varied and context or partner specific (Beery, 2015; Campbell, 2008; Donaldson and Young, 2008; Insel and Young, 2001). Future studies could investigate the mechanisms at play here. Our study does not support the hypothesis that OT acts to facilitate familiarization, and suggests that when administered in house mice during early social interactions with a stranger, OT delays cooperation with that partner during communal nursing.

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